

A<sup>3</sup>  
carrying the mutant isoleucine residue at position 8 were recognized. Maximum half-lysis was obtained with only  $5 \times 10^{-11}$  M of the decapeptide, compared to  $5 \times 10^{-7}$  M of the nonapeptide (Figure 6). 11C2 CTL also recognizes the wild-type decapeptide 286-295 (SLFEGIDFYT) (SEQ ID NO: 7), with a maximum half-lysis of  $5 \times 10^{-8}$  M, but not the wild-type nonapeptide 286-294 (Figure 6).

**IN THE CLAIMS:**

Please cancel claim 32 without prejudice to or disclaimer of the subject matter contained therein.

Please amend claims 1-31 and 33-46 as follows:

A<sup>4</sup>  
1. (Amended) A method for identifying a peptide compound derived from a natural hsp70 sequence, the compound having at least one mutation or modification with respect to the natural hsp70 sequence and bringing about a T response specific for tumors, comprising:

- a) PCR-amplifying a DNA fragment encoding hsp70, obtained from at least one tumor,
- b) cloning the DNA obtained in step a) into a vector capable of replicating in a bacterium,
- c) sequencing a peptide fragment in each bacterial colony obtained after culturing the bacteria of step b), and identifying the at least one mutation in hsp70, and
- d) determining the immunogenicity of the peptide fragment having at least one mutation or modification among those identified in step c).

LAW OFFICES

FINNEGAN, HENDERSON,  
FARABOW, GARRETT,  
& DUNNER, L.L.P.  
1300 I STREET, N. W.  
WASHINGTON, DC 20005  
202-406-4000

2. (Amended) The method as claimed in claim 1, wherein the immunogenicity of the peptide fragment in step d) is determined in an Elispot assay.

3. (Amended) The method as claimed in claim 1, wherein the immunogenicity of a peptide fragment having an anchoring sequence for a given HLA molecule is tested in step d).

4. (Amended) The method as claimed in claim 1, wherein the peptide to be tested in step d) is obtained by chemical synthesis.

5. (Amended) A method for revealing artificial point mutations or modifications, which can increase the immunogenicity of a mutated peptide compound derived from hsp70, comprising:

- A4
- a) determining fragments which have a sequence of from 9 to 10 amino acids comprising an anchoring motif for a given HLA molecule,
  - b) introducing an additional point mutation or modification at residues chosen from 4, 5, 6, 7 and 8, and
  - c) determining the immunogenicity of the peptide fragment obtained in step b).

6. (Amended) The method as claimed in claim 5, wherein the immunogenicity of the peptide fragment in step c) is determined in an Elispot assay.

7. (Amended) A peptide compound obtained using a method as claimed in claim 1 comprising a sequence of at least 8 consecutive amino acids of a natural hsp70 sequence, the sequence having at least one mutation or modification with respect to the natural hsp70 sequence, and wherein the peptide compound brings about a specific T response.

LAW OFFICES

FINNEGAN, HENDERSON,  
FARABOW, GARRETT,  
& DUNNER, L.L.P.  
1300 I STREET, N. W.  
WASHINGTON, DC 20005  
202-408-4000

Sub C2  
8. (Amended) The peptide compound as claimed in claim 7, having at least 80% homology with amino acids between positions 286 and 294 of the natural hsp70 sequence.

9. (Amended) The peptide compound as claimed in claim 8, wherein the amino acid at position 293 is chosen from isoleucine, leucine, valine, alanine, glycine, and phenylalanine.

10. (Amended) The peptide compound as claimed in claim 9, comprising at least one sequence chosen from SEQ ID No. 1 and SEQ ID No. 2.

A4 ab 2  
11. (Amended) The peptide compound as claimed in claim 7, comprising at least one element other than natural amino acids.

12. (Amended) A DNA fragment encoding at least a fragment of the peptide compound of claim 7.

amb 3  
13. (Amended) A vector for expressing the peptide compound as claimed in claim 7, comprising a DNA fragment encoding a peptide fragment, wherein the DNA fragment is fused to a promoter which is strong and effective in eukaryotic and/or in prokaryotic cells.

14. (Amended) The vector as claimed in claim 13, further comprising at least one selection marker and, optionally, at least one coding sequence for factors which activate immune defenses.

mb 17  
15. (Amended) The vector as claimed in claim 13, wherein the vector is chosen from a viral vector, a plasmid, and a pseudovector.

16. (Amended) A dendritic cell loaded with a peptide compound as claimed in claim 7.

LAW OFFICES

FINNEGAN, HENDERSON,  
FARABOW, GARRETT,  
& DUNNER, L.L.P.  
1300 I STREET, N. W.  
WASHINGTON, DC 20005  
202-408-4000

17. (Amended) A dendritic cell transformed with a vector as claimed in claim 13.

18. (Amended) The dendritic cell as claimed in claim 16, wherein the dendritic cell is a macrophage.

19. (Amended) A pharmaceutical composition comprising a peptide compound, or a mixture of peptide compounds, as claimed in claim 7 and a pharmaceutically acceptable vehicle.

20. (Amended) The pharmaceutical composition as claimed in claim 19, further comprising at least one immunological adjuvant.

21. (Amended) A pharmaceutical composition comprising a vector as claimed in claim 13 and a pharmaceutically acceptable vehicle.

22. (Amended) A pharmaceutical composition comprising a DNA fragment as claimed in claim 12 and a pharmaceutically acceptable vehicle.

23. (Amended) A pharmaceutical composition comprising the dendritic cell as claimed in claim 16 and a pharmaceutically acceptable vehicle.

24. (Amended) A combination product comprising at least one peptide compound as claimed in claim 7 and at least one agent which induces cellular stress, for simultaneous or separate use, or for use spread out over time, for treating cancer.

25. (Amended) The combination product as claimed in claim 24, wherein said at least one agent is capable of inducing overexpression of heat shock proteins.

26. (Amended) The combination product as claimed in claim 24, wherein said at least one agent is an apoptosis inducer, chosen from DNA-damaging agents, glucocorticoid receptor ligands, and pro-apoptotic second messengers.

LAW OFFICES

FINNEGAN, HENDERSON,  
FARABOW, GARRETT,  
& DUNNER, L.L.P.  
1300 I STREET, N. W.  
WASHINGTON, DC 20005  
202-408-4000

27. (Amended) The combination product as claimed in claim 24, comprising a viral vector which has a gene which encodes an enzyme for activating pro-apoptotic agents.

28. (Amended) The combination product as claimed in claim 24, wherein the at least one agent which induces cellular stress is chosen from compounds which induce tumor hypoxia.

29. (Amended) The combination product as claimed in claim 24 further comprising at least one immunological adjuvant.

30. (Amended) The pharmaceutical composition as claimed in claim 19 further comprising a pharmaceutical vehicle which is compatible with IV, subcutaneous, oral or nasal administration.

31. (Amended) The pharmaceutical composition as claimed in claim 19 further comprising a pharmaceutical vehicle chosen from positively charged liposomes, negatively charged liposomes, nanoparticles, and lipid emulsions.

33. (Amended) A method for treating cancer comprising administering to a patient a medicinal product comprising a peptide compound comprising a sequence of at least 8 consecutive amino acids of a natural hsp 70 sequence, the sequence having at least one mutation or modification with respect to the natural hsp 70 sequence, and wherein the peptide compound brings about a specific T response.

34. (Amended) A method for immunizing ex situ comprising administering to a patient a medicinal product comprising a peptide compound comprising a sequence of at least 8 consecutive amino acids of a natural hsp 70 sequence the sequence having

A4

mb  
elt

A5

Sub  
C5

LAW OFFICES

FINNEGAN, HENDERSON,  
FARABOW, GARRETT,  
& DUNNER, L.L.P.  
1300 I STREET, N. W.  
WASHINGTON, DC 20005  
202-408-4000

at least one mutation or modification with respect to the natural hsp 70 sequence, and wherein the peptide compound brings about a specific T response.

Sub  
C5

35. (Amended) A method for immunizing in situ comprising administering to a patient a medicinal product comprising a peptide compound comprising a sequence of at least 8 consecutive amino acids of a natural hsp 70 sequence the sequence having at least one mutation or modification with respect to the natural hsp 70 sequence, and wherein the peptide compound brings about a specific T response.

AS

36. (Amended) The method as claimed in claim 33, wherein the cancer is chosen from solid tumors, carcinomas, melanomas, neuroblastomas, neck cancers, and head cancers.

37. (Amended) A method for increasing, in culture medium, a tumor CTL population and/or inducing secretion by said CTLs of cytotoxic factors comprising providing a peptide compound comprising a sequence of a least 8 consecutive amino acids of a natural hsp 70 sequence the sequence having at least one mutation or modification with respect to the natural hsp 70 sequence, and wherein the peptide compound brings about a specific T response.

38. (Amended) A method for stimulating immune defenses comprising providing a peptide compound comprising a sequence of at least 8 consecutive amino acids of a natural hsp 70 sequence the sequence having at least one mutation or modification with respect to the natural hsp 70 sequence, and wherein the peptide compound brings about a specific T response.

39. (Amended) The method as claimed in claim 33, in combination with radiotherapy.

LAW OFFICES

FINNEGAN, HENDERSON,  
FARABOW, GARRETT,  
& DUNNER, L.L.P.  
1300 I STREET, N. W.  
WASHINGTON, DC 20005  
202-408-4000

40. (Amended) A method for performing repeated immunization for the purpose of causing a breakdown of tolerance against the corresponding natural peptide (nonmutated) in a patient comprising administering to the patient a peptide compound, comprising a sequence of at least 8 consecutive amino acids of a natural hsp 70 sequence, the sequence having at least one mutation or modification with respect to the natural hsp 70 sequence, and wherein the peptide compound brings about a specific T response.

41. (Amended) A method for producing an antibody which binds to an hsp70 mutant comprising:

AS  
a) immunizing a mammal with a peptide compound in claim 7, comprising a sequence of at least 8 consecutive amino acids of a natural hsp 70 sequence, the sequence having at least one mutation or modification with respect to the natural hsp 70 sequence, and wherein the peptide compound brings about a specific T response and

b) isolating a monoclonal antibody which binds to hsp70-2-293 in an immunological assay.

42. (Amended) A monoclonal antibody which binds to a mutated-hsp70 fragment.

43. (Amended) A method for detecting mutated hsp70 comprising:

a) contacting a sample taken from an individual with a monoclonal antibody as claimed in claim 42,

b) allowing the formation of an antibody/mutated hsp70 complex and

c) detecting mutated hsp70 by means of a detectable label which is in the complex or which binds to the complex.

LAW OFFICES

FINNEGAN, HENDERSON,  
FARABOW, GARRETT,  
& DUNNER, L.L.P.  
1300 I STREET, N. W.  
WASHINGTON, DC 20005  
202-408-4000

44. (Amended) A diagnostic kit for detecting cancer comprising an antibody as claimed in claim 42.

45. (Amended) A diagnostic kit for the prognosis of established cancer in an individual comprising an antibody as claimed in claim 42.

46. (Amended) A pharmaceutical composition comprising a monoclonal antibody as claimed in claim 42 and a pharmaceutically acceptable vehicle.

Please add new claims 47-63 as follows:

47. (New) The method as claimed in claim 5, wherein the additional point mutation or modification is a post-translational modification.

48. (New) The peptide compound as claimed in claim 9, wherein the amino acid at position 293 is isoleucine.

49. (New) The vector as claimed in claim 13, wherein the promoter is strong and effective in human cells.

50. (New) The vector as claimed in claim 14, wherein the factors which activate the immune defenses are chosen from cytokines and lymphokines.

51. (New) The pharmaceutical composition as claimed in claim 20, wherein the at least one immunological adjuvant is a factor which is cytotoxic for tumors.

52. (New) The combination product as claimed in claim 25, wherein the heat shock proteins are hsp70.

53. (New) The combination product as claimed in claim 27, wherein the pro-apoptotic agents are thymidine kinases.

LAW OFFICES

FINNEGAN, HENDERSON,  
FARABOW, GARRETT,  
& DUNNER, L.L.P.  
1300 I STREET, N. W.  
WASHINGTON, DC 20005  
202-408-4000

54. (New) The combination product as claimed in claim 28, wherein the compounds which induce tumor hypoxia are angiogenesis inhibitors.

55. (New) The combination product as claimed in claim 29, wherein the at least one immunological adjuvant is an agent which is cytotoxic for tumors.

56. (New) The combination product as claimed in claim 24, further comprising a pharmaceutical vehicle which is compatible with IV, subcutaneous, oral or nasal administration.

57. (New) The combination product as claimed in claim 24, wherein the pharmaceutical composition as claimed in claim 19 further comprising a pharmaceutical vehicle chosen from positively charged liposomes, negatively charged liposomes, nanoparticles, and lipid emulsions.

58. (New) The method as claimed in claim 36, wherein the cancer is a renal carcinoma.

59. (New) The method as claimed in claim 37, wherein the cytotoxic factors are chosen from IC-2, IFN- $\gamma$ , and TNF.

60. (New) The method as claimed in claim 41, wherein the antibody binds to an hsp70-2 I-293 mutant.

61. (New) The monoclonal antibody as claimed in claim 42, wherein the mutated-hsp70 fragment is hsp70-2 I-293.

62. (New) The method as claimed in claim 43, wherein the mutated hsp70 is hsp70-2 I-293.

63. (New) The method as claimed in claim 43, wherein the antibody/mutated hsp complex is an antibody/hsp70-2-293 complex.

LAW OFFICES

FINNEGAN, HENDERSON,  
FARABOW, GARRETT,  
& DUNNER, L.L.P.  
1300 I STREET, N. W.  
WASHINGTON, DC 20005  
202-408-4000

ADD  
C6